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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/720,435	06/25/2001	Lieven Stuyver	11362.0030.P	1489

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Patricia A Kammerer
Howrey Simon Arnold & White
750 Bering Drive
Houston, TX 77057-2198

EXAMINER	
EINSMANN, JULIET CAROLINE	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 03/14/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/720,435	STUYVER, LIEVEN	
	Examiner	Art Unit	
	Juliet C Einsmann	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/2/02; 12/24/02* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-8,12-21 and 23-33* is/are pending in the application.

4a) Of the above claim(s) *7,8,12-21,23-29,32 and 33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 4, 5, 6, 30, and 31,* is/are rejected.

7)☒ Claim(s) *31* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2a* .
4) ☒ Interview Summary (PTO-413) Paper No(s). *18* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1, 3, 4, 5, 6, 7, 8, 13, 14, 15, 16, 28, 29, 30, 31, 32, and 33, drawn to methods for determining the susceptibility to antiviral drugs of HIV viruses in a biological sample.

Group II, claim(s) 12, 17, 18, 19, 20, 21, 23, 24, 25, 26, and 27, drawn to kits, solid supports, and compositions comprising at least two probes fixed to a solid support wherein said probes are capable of specifically and simultaneously hybridizing to a target sequence of the HIV protease gene.

2. The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The technical feature which joins the two groups is that the methods utilize and the compositions comprise "at least two probes specifically hybridizing to a target sequence of the HIV protease gene, codon 82/84...wherein said probes are immobilized on a solid support." This technical feature does not provide a special technical feature over the prior art as is required in the PCT rules in order to establish unity of invention.

For example, Kozal *et al.* (Nature Medicine, Volume 2, Number 7, July 1996) provide a solid support that comprises multiple probes that hybridize to codons 82 and 84 of the HIV protease gene, and use the solid support to detect mutations present in HIV viruses from biological samples. Thus, groups I and II are not joined by a special technical feature that provides a contribution over the prior art, and the two groups are properly separated from one another.

3. This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species are as follows:

Each group above contains a multitude of species of inventions.

(a) The claims encompass multiple groupings of codons for which are recited for both the method claims and the product claims. All claims minimally require codons 82/84. Additional dependent claims recite a multitude of other possible groupings of codons. Each possible grouping of codons is considered a separate species of invention.

(b) The claims recite a multitude of possible probes (identified by SEQ ID NO) to be attached to a solid support.

(c) The claims recite multiple possible primer pairs identified by different SEQ ID NO.

Applicant is required, in reply to this action, to elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

The following claim(s) are generic insofar as they do not recite particular SEQ ID NOs: 1, 5, 6, 20, 25, 26, 27, 28, and 31. Some of these do recite multiple possible groupings of target codons.

4. The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: The special technical feature that joins these species is that they are probes to particular codons of the HIV protease genes, wherein the codons contain mutations that cause resistance to protease inhibitors. However, such probes were known in the art at the time the invention was made (see for example Eastman *et al.* Journal of Virology, Vol. 72, No. 6, pages 5154-6164), and this is not a special technical feature that distinguishes the probes used in the instant methods from the prior art. Thus, the requirement of an election of a single species for examination is proper.

5. During a telephone conversation with Patricia Kammerer on 1/28/03 a provisional election was made with traverse to prosecute the invention of group I, claims 1, 3, 4, 5, 6, 30, and 31, with respect to the codons 82/84, particular elected probes SEQ ID NO: 267 and SEQ ID NO: 354, primer pair SEQ ID NO: 3 and SEQ ID NO: 4. Affirmation of this election must be

made by applicant in replying to this Office action. Claims 7, 8, 13, 14, 15, 16, 12, 17, 18, 19, 20, 21, 23, 24, 25, 26, 27, 28, 29, 32, and 33 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

6. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Objections

7. Claim 31 is objected to because of the following informalities: The claim refers to figure 1. Furthermore, claim MPEP 2173(s) states "Where possible, claims are to be complete in themselves. Incorporation by reference to a specific figure or table "is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim. Incorporation by reference is a necessity doctrine, not for applicant's convenience." In the instant case, the figure recites a multitude of nucleic acid sequences that can be represented by sequence identifier. Appropriate correction is required.

Specification

8. The disclosure is objected to because of the following informalities:

The tables are not numbered sequentially throughout the specification.

Appropriate correction is required.

9. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reason(s): The specification and figures recite nucleotide sequences that are not properly identified by sequence identifiers (see, for example, specification page 21, line 23 and figures 1, 2, and 3)

In order to comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825), Applicant must submit, ***as necessary***, a new CRF and paper copy of the Sequence Listing containing these sequences, in addition to the previously listed sequences, an amendment directing the entry of the Sequence Listing into the specification, an amendment directing the insertion of the SEQ ID NOs into the appropriate pages of the specification and a letter stating that the content of the paper and computer readable copies are the same.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1, 3, 4, 5, 6, 30, and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and those claims that depend from claim 1 are indefinite because both steps (a) and (b) are recited as being optional (i.e. performed "if need be"), yet step (c) requires the nucleic acid of step (a) or (b) for hybridization with the recited at least two probes, thus, step (c)

implies that at least on of steps (a) or (b) must be carried out, but steps (a) and (b) are not consistent with this implication. Thus, the claim is unclear as to which steps are required.

In claim 1, step (a), the phrase "the polynucleic acids" lacks proper antecedent basis because the claim does not previously refer to polynucleic acids.

In claim 1, step (b), the phrase "the relevant part of a protease gene" lacks proper antecedent basis because the claim does not previously refer to a "relevant" part of the protease gene. Further, the phrase "relevant part" is indefinite because it is not clear what makes a portion of the protease gene relevant in this context.

Claim 1 and those claims that depend from claim 1 are indefinite over the recitation "codon 82/84" because it is not clear if this means that the probes must hybridize to codon 82 and 84 or if this means that the probes must hybridize to codon 82 or codon 84. It is not clear if the use of a probe that hybridizes to one but not the other is encompassed within the scope of the instant claims. Clarification is required.

In claim 1, part (d), "said target sequences" lacks proper antecedent basis because the claim previously refers to a singular target sequence (in part (c)) but the claim does not previously refer to multiple target sequences.

Claims 5 and 6 are indefinite because they recite that step (b) comprises amplifying a fragment, but it is not clear if this step (b) recited in claims 5 and 6 is meant to replace the step (b) in claim 1 or is meant to merely define the amplifying that is to take place "if need be." That is, it is not clear if the amplification recited in claims 5 and 6 is required to take place in the method or if the amplification discussed in claims 5 and 6 is to take place "if need be" as is recited in the independent claim.

Claims 5 and 6 are further indefinite over the recitation of specific nucleotide positions in the protease gene, for example, the recitation "located at nucleotide position 210-260 of the protease gene" because such positions are entirely arbitrary when they are recited without particular reference to a recitation of the protease gene. The nucleotide positions in a recitation of the gene are entirely context dependent on a given disclosure of the gene, whether the disclosure provides 5' untranslated regions, includes introns, is within the context of the entire HIV genome, etc. It is not known from the recitations in the claims what the context for the numbering used in the claims is, and thus the metes and bounds of the required primers is unclear.

Claim 31 is indefinite over the recitation "wherein the target sequences for codon 82/84 are shown in Figure 1" because it is not clear what target sequence referred to in Figure 1 is intended to be the target sequence, and further, it is not clear if this claim is requiring that the target sequences be each of the possible variations listed in table 1 or some subset of the variations. Furthermore, Figure 1 itself is not clear, listing for codons 82 and 84 a wide variety of possible sequences. It is not clear if the "target sequence" depicted in the second line of the Codon 82/84 section must contain each of the variations recited in that line, or if each variation taken individually within the sequence listed in the first line is intended. Clarification is required.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Kozal *et al.* (Nature Medicine, 1996, Volume 2, Number 7, pages 753-759).

Kozal *et al.* teach a method for determining the susceptibility to antiviral drugs of HIV viruses in a biological sample, with said method comprising:

(a) releasing the polynucleic acids present in the sample (via lysis, p. 758);

(b) amplifying the relevant part of a protease gene of HIV with at least one suitable primer pair (p. 758);

(c) hybridizing the polynucleic acids of step (b) with at least two probes specifically hybridizing to a target sequence of the HIV protease gene codon 82/84, wherein said probes are capable of simultaneously hybridizing to their respective targets under appropriate hybridization and wash conditions, wherein said probes are immobilized on a solid support;

(d) inferring from the result of (c) whether or not a mutation giving rise to drug resistance is present in said target sequences (p. 758 and Fig. 1).

Specifically, Kozal *et al.* teach a method in which amplified portions of the HIV protease gene are sequenced by hybridization to a solid support (referred to as a chip), wherein a set of four 15-base oligonucleotide probes differing at the 7 nucleotide position is used to determine the identity of each base in the protease gene (Fig. 3 and p. 758). Using this methodology, Kozal *et al.* detected the presence of mutations at codon 82 of the protease gene that confers resistance to antiviral drugs (see Figure 1).

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 1, 3, 5, 6, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stuyver *et al.* (WO 97/27332) in view of Eastman *et al.* (Journal of Virology, June 1998, p. 5154-5164).

Stuyver *et al.* teach a method for determining the susceptibility to antiviral drugs of HIV viruses in a biological sample, with said method comprising:

(a) releasing the polynucleic acids present in the sample;

(b) amplifying the relevant part of a gene of HIV with at least one suitable primer pair;

(c) hybridizing the polynucleic acids of step (b) with at least two probes specifically hybridizing to a target sequence of a HIV gene, wherein the target sequence includes codons known to have mutations which lead to antiviral drug resistance, wherein said probes are capable of simultaneously hybridizing to their respective targets under appropriate hybridization and wash conditions, wherein said probes are immobilized on a solid support;

(d) inferring from the result of (c) whether or not a mutation giving rise to drug resistance is present in said target sequences (see p. 4, line 15- p. 5, line 16).

Specifically, the methods taught by Stuyver *et al.* are directed at detecting drug-induced mutations in the HIV reverse-transcriptase gene, and thus Stuyver *et al.* do not specifically exemplify methods in which the HIV protease gene is optionally amplified or hybridized to

probes. Stuyver *et al.* do, however teach that one of the advantages of their test is that it can "easily" be extended to include the proteinase codons associated with resistance (see p. 29, lines 29-31). Nonetheless, Stuyver *et al.* do not teach a method utilizing probes that hybridize to codon 82/84 of the protease (also referred to as proteinase) gene.

Eastman *et al.* teach methods for detecting genotypic changes in HIV associated with loss of susceptibility to antiviral drugs, specifically teaching a hybridization method which utilizes multiple probes to codon 82 and codon 84 of the HIV protease gene (see p. 5155, Col. 2 and Table 1).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the probes taught by Eastman *et al.* in the methods taught by Stuyver *et al.* The ordinary practitioner would have been motivated to look to the teachings of Eastman *et al.* for probes to codon 82/84 of the HIV protease gene because Stuyver *et al.* specifically teach that their method could easily be extended to include protease codons associated with antiviral drug resistance, and Eastman *et al.* teach hybridization probes that have been successfully used to probe such mutations in codons 82/84 of the HIV protease gene. Thus, in light of the teachings of Stuyver *et al.* in view of Eastman *et al.*, the instant invention is prima facie obvious in view of the prior art.

With respect to claims 5 and 6, these claims are previously rejected as being indefinite because it is not known precisely what regions of the protease gene are being referred to by the claims. This problem is highlighted by the fact that Eastman *et al.* are using what appear to be an entirely different numbering system than applicant's to refer to positions in the HIV protease gene (see Table 1 of Eastman *et al.* for example). Insofar as claims 5 and 6 require that the

primers be upstream and downstream of the interrogated codon, it would have been prima facie obvious in view of the prior art to select primers that are upstream and downstream of codons 82 and 84 in order to provide primers that would lead to amplification of the relevant region of the HIV protease gene.

Conclusion

16. A species election was set forth requiring applicant to select a method using a single pair of probes to which the claims shall be restricted if no generic claim is finally held to be allowable. In response, applicant elected a method which utilizes a pair of probes consisting of SEQ ID NO: 267 and SEQ ID NO: 354. This method is free of the prior art. The prior art does not teach or suggest an oligonucleotide probe that has the sequence of SEQ ID NO: 354. Additional species have not been searched because there is no allowable generic claim. (See the species election which states that applicant is required to elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable). However, it is further noted that Eastman *et al.* teach oligonucleotide probes that consist of instant SEQ ID NO: 327 and SEQ ID NO: 324 (probes V82F MUT and I84 WT, respectively).

17. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

(A) Condra *et al.* (Journal of Virology, 1996, pages 8270-8276, Vol. 70, No. 12) disclose the nucleotide sequences of the HIV protease gene from patients that have mutations causing antiviral drug resistance. Condra *et al.* provide GenBank U71659, which comprises instant SEQ ID NO: 267 at positions 238 through 252 (the GenBank record has been attached to the paper for

Applicant's convenience). This segment of the protease gene overlaps with codon 82 of patient C, who exhibited the V82A mutation (see p. 8272).

(B) Markowitz *et al.* (Journal of Virology, 1995, pages 701-706, Vol. 69, No. 2) discloses a HIV protease variant that has an isoleucine to valine substitution at position 84 and an additional mutation at position 82, valine to phenylalanine. These substitutions are targeted using SEQ ID NO: 354. Markowitz *et al.* do not teach or suggest a codon encoding methionine at position 85 as is encoded in SEQ ID NO: 354 (the wild type HIV protease has isoleucine at position 85, see Markowitz *et al.* Figure 2).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C. Einsmann whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

JEFFREY FREDMAN
PRIMARY EXAMINER

Juliet C. Einsmann
Examiner
Art Unit 1634

March 10, 2003